PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

CO-IPRASAL SOLUTION (solution for inhalation)

COMPOSITION:

Each 2,5 ml unit dose vial contains 0,5 mg ipratropium bromide and 3,0 mg salbutamol sulphate, (equivalent to 2,5 mg salbutamol base).

Other ingredients:

Hydrochloric acid, sodium chloride, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 10.2.1 Medicines acting on respiratory system. Inhalants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ipratropium is a quaternary ammonium compound with anticholinergic (parasympathetic) properties which inhibits vagally medicated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Salbutamol sulphate is a beta$_2$-adrenergic medicine which acts on airway smooth muscle resulting in relaxation.

The simultaneous delivery of ipratropium bromide and salbutamol sulphate allows stimulation of both muscarinic and beta$_2$-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each medicine singly.

Pharmacokinetic properties:

Absorption:

Ipratropium bromide is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastro-intestinal tract as determined by blood level and renal excretion studies.

Salbutamol sulphate is rapidly and completely absorbed following oral administration either by the inhaled or gastric route.

It has been shown that co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component.

Distribution:

Ipratropium bromide does not cross the blood-brain barrier.

Intravenous salbutamol will cross the blood-brain barrier reaching concentrations amounting to about five percent of the plasma concentration.

Elimination:

The elimination half-life of ipratropium bromide is about 3 - 4 hours after inhalation or

intravenous administration.

Peak plasma salbutamol concentrations are seen within three hours of administration and the medicine is excreted unchanged in the urine after 24 hours. The elimination half-life is 4 hours.

INDICATIONS:

CO-IPRASAL SOLUTION is indicated for the management of reversible bronchospasm associated with obstructive pulmonary disease.

CONTRAINDICATIONS:

CO-IPRASAL SOLUTION is contraindicated in patients with cardiac tachydysrhythmias, hypertrophic obstructive cardiomyopathy and in patients with a history of hypersensitivity to any of its components or to atropine or its derivatives.

There is no experience of the use of **CO-IPRASAL SOLUTION** in children under the age of 12 years.

WARNINGS AND SPECIAL PRECAUTIONS:

- Immediate hypersensitivity reactions may occur after administration of **CO-IPRASAL SOLUTION**, e.g. urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.
- There have been reports of ocular complications (i.e. mydriasis, increased intraocular pressure, acute angle glaucoma, eye pain) when nebulised ipratropium bromide either alone or in conjunction with a $beta_2$- agonist, has escaped into the eyes.
- Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion may be signs of acute narrow-angle

glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

- Patients must be instructed in the correct use of **CO-IPRASAL SOLUTION**. Care must be taken not to expose the eyes to the solution or mist of **CO-IPRASAL SOLUTION**. It is recommended that the nebulised solution be administered via a mouthpiece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.
- The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

In the following conditions **CO-IPRASAL SOLUTION** should only be used after careful risk/benefit assessment: inadequately controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy, urinary retention, or bladder-neck obstruction.

Myocardial ischaemia has been associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, severe heart failure) who are receiving salbutamol for respiratory disease, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea.

The concomitant use of **CO-IPRASAL SOLUTION** with other sympathomimetic medicines is not recommended since such combined use may lead to deleterious cardiovascular effects (see **INTERACTIONS**).

If higher than recommended doses of **CO-IPRASAL SOLUTION** are required to control symptoms, the patient's therapy plan should be reviewed by a doctor.

The maximum dose should not be exceeded.

Potentially serious hypokalaemia may result from beta$_2$-antagonist therapy.

Particular caution is advised in severe airway obstruction, as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics (see **INTERACTIONS**). Additionally, hypoxia and acidosis may aggravate the effects of hypokalaemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy such as **CO-IPRASAL SOLUTION**, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see **SIDE EFFECTS** and **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**).

Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification

of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Effects on ability to drive and use machines:

CO-IPRASAL SOLUTION may result in visual disturbances and dizziness which may impair the ability to drive or operate machinery.

INTERACTIONS:

Xanthine derivatives (e.g. theophylline) and beta$_2$-adrenergic medicines and anticholinergics may enhance the effects of **CO-IPRASAL SOLUTION** inhalation (see **WARNINGS AND SPECIAL PRECAUTIONS**).

CO-IPRASAL SOLUTION induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids, and diuretics. This should be taken into account particularly in patients with severe airway obstruction (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Hypokalaemia may result in an increased susceptibility to dysrhythmias in patients receiving digoxin.

Other sympathomimetic bronchodilators or epinephrine (adrenaline) should not be used concomitantly with **CO-IPRASAL SOLUTION**. If additional adrenergic medicines are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects. Such concomitant use must be individualised and not given on a routine basis. If regular

co-administration is required, then alternative therapy must be considered (see **WARNINGS AND SPECIAL PRECAUTIONS**).

CO-IPRASAL SOLUTION should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of salbutamol on the vascular system may be potentiated.

There is an increased risk of dysrhythmias if administered concomitantly with cardiac glycosides, quinidine or tricyclic antidepressants. **CO-IPRASAL SOLUTION** should not be given to patients receiving mono-amine oxidase inhibitors or within 14 days of termination of monoamine oxidase inhibitor therapy.

Beta-receptor blocker medicines and salbutamol inhibit the effects of each other.

Inhalation of halogenated hydrocarbon anaesthetics may increase the susceptibility to the cardiovascular effects of beta-agonists.

It is strongly recommended not to mix **CO-IPRASAL SOLUTION** with other medicines in the same nebuliser.

Anticholinergic effects of other medicines may be enhanced.

HUMAN REPRODUCTION:

The safety of **CO-IPRASAL SOLUTION** in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

CO-IPRASAL SOLUTION for inhalation may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.

The recommended dose is:

Adults (including elderly patients) and children over 12 years:

Treatment of acute attacks:

1 unit dose vial is sufficient for prompt symptom relief in many cases.

In severe cases, if an attack has not been relieved by one unit dose vial, two unit dose vials may be required. In these cases, patients should consult their doctor or nearest hospital immediately.

Maintenance treatment:

1 unit dose vial three or four times daily.

There is no experience in the use of **CO-IPRASAL SOLUTION** in children under 12 years of age.

Do not exceed the recommended dose.

Dilution instructions:

If necessary, before use, doses may be diluted to a total nebulisation volume of 3-5 ml with preservative free 0,9 % sterile sodium chloride solution and used immediately. Discard any

unused solution. Nebulise over 10-15 minutes at gas flow of 6-10 l/min. Repeat every six hours as necessary.

Instructions for use:

The unit dose vials are intended for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or your doctor.
2. Tear one unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the contents of the unit dose vial into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.
6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.

It is strongly recommended not to mix **CO-IPRASAL SOLUTION** for inhalation with other medicines in the same nebuliser reservoir.

If dilution is necessary, this should be carried out using ONLY sterile sodium chloride 0,9 % solution and as instructed by your doctor.

SIDE EFFECTS:

Immune system disorders:

Less frequent: Anaphylactic reaction, hypersensitivity, angioedema

Metabolism and nutrition disorders:

Frequency unknown: Hypokalaemia, lactic acidosis

Psychiatric disorders:

Less frequent: Nervousness

Frequency unknown: Mental disorder

Nervous system disorders:

Less frequent: Dizziness, headache, tremor

Eye disorders:

Frequent: Accommodation disorders

Frequency unknown: Angle closure glaucoma, eye pain, increased intraocular pressure, mydriasis, blurred vision

There have been reports of ocular complications with symptoms mentioned above when **CO-IPRASAL SOLUTION** has escaped into the eyes.

Cardiac disorders:

Less frequent: Tachycardia, palpitations, atrial fibrillation, dysrhythmia, myocardial ischaemia

Vascular disorders:

Less frequent: Increased systolic blood pressure, peripheral vasodilatation

Frequency unknown: Decreased diastolic blood pressure

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dysphonia, cough, paradoxical bronchoconstriction,

bronchospasm, pharyngeal oedema

Frequency unknown: Bronchospasm, laryngospasm, throat irritation, pharyngeal oedema

Gastrointestinal disorders:

Frequent: Dry mouth

Less frequent: Nausea, stomatitis

Frequency unknown: Gastrointestinal motility disorder (diarrhoea, nausea, vomiting), oropharyngeal oedema

Skin and subcutaneous tissue disorders:

Frequency unknown: Angioedema, hyperhidrosis, rash, skin reaction, urticaria

Musculoskeletal and connective tissue disorders:

Frequency unknown: Muscular weakness, myalgia, muscle spasms

Renal and urinary disorders:

Frequency unknown: Urinary retention

General disorders and administration site conditions:

Less frequent: Asthenia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The effects of overdose with **CO-IPRASAL SOLUTION** are expected to be related primarily to salbutamol because acute overdose with ipratropium bromide is unlikely since ipratropium bromide is not well absorbed systemically after aerosol or oral administration. Expected symptoms of overdose with ipratropium bromide (such as dry mouth, visual accommodation disturbances) are mild and transient in nature. However, should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

The expected symptoms with overdose are those of excessive beta-adrenergic stimulation, such as: tachycardia, palpitations, tremor, cardiac dysrhythmia, hypokalaemia, hypertension, hypotension, widening of pulse pressure, anginal pain, flushing and in extreme cases, sudden death.

Administration of sedatives, tranquillisers or in severe cases, intensive therapy may be appropriate for the treatment of overdose. To antagonise the effect of salbutamol, the judicious use of a cardioselective beta-adrenergic blocking medicine, (e.g. metoprolol, atenolol), may be

considered, bearing in mind the danger of inducing an asthmatic attack. Serum potassium levels should be monitored.

Metabolic acidosis has also been observed with overdosage of salbutamol, including lactic acidosis which has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnoea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

IDENTIFICATION:

Clear, colourless to pale yellow solution.

Free from visible particles.

PRESENTATION:

A carton containing 2 x 10 strips of 2,5 ml solution (packed in 3 ml ampoules). The 10 strips of the 2,5 ml unit are contained in aluminium overwraps.

STORAGE INSTRUCTIONS:

Store at or below 25 °C protected from light.

The ampoule should be opened immediately before use and any solution remaining after use should be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

41/10.2.1/0765

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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